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Review Article

Diet, sleep, and exercise in inflammatory skin diseases

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ABSTRACT

Inflammatory skin conditions are significantly impacted by lifestyle habits, particularly those related to diet, exercise, and sleep. Although ancient cultures emphasized the importance of lifestyle behaviors as both etiology and therapy in disease, modern medicine often overlooks nonpharmacological therapy. However, recent studies show that diet can have a significant impact on inflammatory skin diseases such as psoriasis, hidradenitis suppurativa, and atopic dermatitis. Foods high in glycemic index, advanced glycation end-products, and omega-6 polyunsaturated fatty acids are associated with obesity and systemic inflammation, which can exacerbate inflammatory skin diseases. In addition, lifestyle behaviors such as exercise and sleep have been shown to have positive effects on inflammatory skin diseases. This review aims to highlight the importance of lifestyle behaviors in the context of inflammation and inflammatory dermatoses.

Key words: Diet, Exercise, Sleep, Psoriasis, Inflammation, Skin

INTRODUCTION

Many ancient cultures place a strong emphasis on lifestyle behaviors as both an etiology and therapy in disease, whereas modern medicine focuses on scientific advancements often overlooking nonpharmacological therapy. Despite recent therapeutic advancements, the field of dermatology includes a myriad of heterogeneous, complex inflammatory diseases with which patients experience considerable morbidity and significant unmet need. The role of lifestyle behaviors in inflammatory processes and disease is not well-defined, and their evaluation, adjustment, or alteration is seldom recommended in dermatology. This review focuses on the function of lifestyle behaviors, such as diet, sleep, and exercise in the context of inflammation and inflammatory dermatoses.

PART I. DIET

Inflammatory skin conditions are the most common problem seen in dermatology practice [1]. Numerous studies have demonstrated a positive association between poor diet and worsening of inflammatory skin diseases, such as psoriasis, hidradenitis suppurativa (HS), and atopic dermatitis [BT1] [2-5]. More specifically, foods with a high glycemic index, advanced glycation end-products (AGEs), and omega-6 polyunsaturated fatty acids (PUFAs) are associated with obesity and systemic inflammation [6-9]. High glycemic index foods significantly increase blood glucose levels, stimulating insulin production [6]. Insulin promotes glucose uptake by adipocytes, promoting fat storage, leading to obesity and increased visceral adiposity. Visceral adipose tissue has a higher density of cells and is more biologically active than other forms of fat, producing inflammatory cytokines, such as leptin, resistin, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and monocyte chemoattractant protein-1 [6,10]. Additionally, increased visceral fat is associated with reduced levels of adiponectin and increased insulin resistance mediated through c-Jun N-terminal kinases (JNKs) phosphorylation in adipocytes [11-15]. These metabolic abnormalities

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lead to dysregulated lipolysis in the liver resulting in excessive delivery of fatty acids to hepatocytes [14,15]. With time, development of non- alcoholic fatty liver disease (NAFLD) and subsequent non-alcoholic steatohepatitis (NASH) occurs. These conditions are positively associated with increased serum concentrations of IL-1β, IL-6, TNF-α, c-reactive protein (CRP), and ICAM-1 [16]. Moreover, AGEs, formed by non-enzymatic glycation of macromolecules, bind to receptors for advanced glycation end products (RAGEs), increasing the transcription of IL-6, TNF-α, and CRP [5,8]. Lastly, PUFAs are metabolized into pro-inflammatory eicosanoids, such as prostaglandin E2 and leukotriene B4 [5,6,9,17]. Taken together, obesity, NAFLD, NASH, and specific dietary components promote a pro-inflammatory environment that is thought to exacerbate inflammatory skin disease. It should also be noted that insulin resistance leads to worsening of hyperglycemia and the development of type II diabetes mellitus, contributing to the vicious circle of obesity-related chronic inflammation [18,19].

In psoriasis, obesity and cardiovascular disease (CVD) are related to incidence, severity, and progression of the condition. The pathogenesis of psoriasis is driven by aberrant TNF-α/IL-23/IL-17 axis signaling, leading to hyperproliferation and increased differentiation of epidermal keratinocytes [20]. Specifically, TNF-α acts on dendritic cells to increase the transcription of IL-23, thereby stimulating T-helper 17 cells to release IL-17A. Through increased TNF-α production, obesity promotes T-helper 17 cell expansion, which also leads to increased IL-17A production, participating in the pathogenesis of psoriasis. Similarly, the link between psoriasis and CVD is thought to be due to shared pro-inflammatory pathways between the two conditions [21,22]. Akin to psoriasis, the pathogenesis of hidradenitis suppurativa (HS) involves hyperactivation of the TNF-α/IL-23/IL-17 axis, preceded by follicular occlusion of the follicular pilosebaceous unit [23]. The prevalence of obesity among HS patients was roughly 2.5 times that of non-HS patients [24]. The number of patients reporting HS symptoms after a 15% weight reduction decreased by 35%, with a statistically significant reduction in the number of body sites involved [25]. Interestingly, the prevalence of obesity and metabolic syndrome is thought to be higher in patients with HS relative to psoriasis with an OR of approximately 6.0 compared to 2.0 [26]. In addition to elevated TNF-α and IL-6 production, metabolic syndrome-induced androgen overproduction of sebum and overgrowth of the intra-ductal keratinocytes is thought to be the backbone of obesity-mediated HS exacerbation. In atopic dermatitis (AD), dietary factors such as cow's milk, egg, soybean, and wheat gluten contribute to symptom progression [27]. In a study by Breuer et al., the mentioned food allergens were administered to 106 pediatric patients with AD [28]. The food challenge triggered immediate onset exanthematous reactions in 46% of participants. Additionally, a cross-sectional study involving approximately 18,000 patients with or without AD identified a significant association between processed food, meat, and instant noodle consumption in those with a diagnosis [29]. Food allergens can trigger acute immunoglobulin E- mediated hypersensitivity reactions or food allergy related T-cell late eczematous reactions [27]. As such, patch testing and dietary modification via a predominantly plant based anti-inflammatory diet is recommended for those with AD [27-30]. The impact of poor diet and obesity on inflammatory skin disease is an important topic of discussion, as it is predicted 50% of adults will have obesity by 2030 [31]. As such, it is logical to assume an increase in the prevalence of inflammatory skin pathologies with time. Additional studies involving dietary intervention on disease remission are warranted.

PART II. SLEEP

The circadian rhythm is an essential internal clock synchronized with the environmental light-dark cycle present in all mammals. In humans, the circadian rhythm is under the control of the suprachiasmatic nucleus and retinohypothalamic tract, and it involves a molecular transcription- translation feedback loop present in most tissues and cell types [32,33]. Skin, an important immunological organ, exhibits a diurnal expression of various proteins within its layers, where the light-dark cycle- related alterations in gene expression are most prominent in the epidermis [34,35]. The immune function of the skin is regulated by circadian rhythms, and its proper function is important for suppression of autoimmune diseases [36,37]. Disturbances in circadian rhythms associated with shift work have been hypothesized to contribute to the development of psoriasis and other autoimmune conditions [33]. The possible contributing factors include decreased levels of melatonin and vitamin D, which are known for their anti-inflammatory effects [31-33]. Additionally, the light-dark cycle controls the function of γδ+ T cells and Langerhans cells within the epidermis, which are important for the immune functions of the skin.

The γδ+ T cells are controlled via a direct activation of the Interleukin-23 (IL-23) promoter by circadian rhythm CLOCK protein within the γδ+ T cell subset [38]. Similarly, macrophages and mast cells of the dermis layer are directly regulated by the circadian clock and mediate phagocytosis and cutaneous anaphylactic reactions, respectively [39]. Other diurnal immunologic skin patterns include circadian cycle-dependent T cell recruitment, which is implicated in nocturnal exaggeration of atopic dermatitis and overall fluctuations in chemoattractant levels throughout the skin layers [36,40].

Circadian cycle disturbances have been repeatedly linked to chronic inflammatory diseases [36,41-46]. Insufficient sleep is known to be associated with chronic inflammatory states seen in diabetes, obesity, and cardiovascular diseases, which are often comorbid with dermatologic autoimmune conditions [46]. Severity of several autoimmune skin conditions including psoriasis is inversely correlated with the amount of sleep and sleep difficulty [47,48]. Sleeping disturbances associated with disease state or pharmacological side effects negatively impact circadian cycle [49,50]. In psoriasis and atopic dermatitis, nocturnal pruritus disturbs sleep and further exacerbates severity of the autoimmune conditions, creating a positive feedback loop [50,51].

The effects of sleep on the immune system include a bidirectional regulation between the stages of the sleep cycle and levels of pro-inflammatory cytokines. Sufficient nighttime sleep is necessary for proper bimodal daily release of IL-6, which plays an important role in acute inflammation. IL-6 is a cytokine with context-dependent pro- and anti-inflammatory properties, and is implicated in cell differentiation, oncogenesis, and pathogenesis of inflammatory skin conditions including psoriasis, vitiligo, and atopic dermatitis [52-54]. Sleep deprivation is correlated with disproportional increase in daytime IL-6 accompanied by a decline in nocturnal IL-6 levels, as well as increased NF-κB activation [55,56]. Alterations of IL-6 and NF-κB functioning further support the role of sleep in the development of inflammatory states. Additionally, a variety of pro-inflammatory cytokines possess sleep-modifying properties [57,58]. For instance, elevated IL-1 and TNF-alpha levels have been associated with a reduction in rapid eye movement (REM) sleep and an increase in total non-REM [59]. Interestingly, sleep deprivation additionally skews the Th1/Th2 phenotypic ratio towards the Th2 dominance [60]. Increased prevalence of the Th2 phenotype, compared to Th1, is implicated in development of dermatologic conditions such as atopic dermatitis, highlighting the possible importance of sleep in autoimmune states. Further investigation is needed to elucidate the effects of molecular players of circadian cycles on the pathogenesis of autoimmune skin conditions.

PART III. EXERCISE

Both aerobic exercise and strength training produce a decrease in inflammation. Interestingly, exercise's true anti-inflammatory effects arise gradually, whereas short-term changes with exercise induce pro-inflammatory processes. The initial response is mediated by an increase in the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, both during and immediately following exercise [61]. However, the transient inflammatory state is counteracted by release of anti-inflammatory hormones cortisol and adrenaline [62,63]. With frequent exercise, the anti-inflammatory effects predominate in a longer-term response.

Though the exact mechanism is unknown, several hypothesized pathways have been proposed. One proposed mechanism is that exercise's anti-inflammatory effects are due to a significant decrease in pro-inflammatory cytokines C-reactive protein (CRP), IL-6, and TNF [62]. Others suggest that exercise activates AMP-activated protein kinase (AMPK), thus increasing fatty acid oxidation and glucose metabolism [64]. Javaid, et al. suggest that beneficial effects of exercise may be explained by inhibition of NLRP3 inflammasome activation by the myokine Meteorin-like (METRNL) which is crucial for the onset of inflammation [65].

In support of exercise's downregulation of TNF-α, a clinical trial investigating exercise's pro-inflammatory effects showed that in participants infused with Escherichia coli, resting participants to have a two- to threefold increase in TNF-α compared to the participants who performed a cycling exercise earlier that day [66,67]. Furthermore, though the exact pathway is unknown, IL-6 appears to play a significant role [62,63,67-81]. IL-6 is commonly classified as a proinflammatory cytokine, much like TNF-α, however studies suggest it may have anti-inflammatory properties as well, due to its ability, via negative feedback, to decrease the body's levels of TNF-α and other proinflammatory cytokines [70,72,76,80]. Levels

of IL-6 may be increased up to 100-fold in long-term exercise [63,74-77]. In fact, participants who did not exercise but were given recombinant human IL-6 (rhIL-6), displayed a similar decrease in levels of TNF-α, as participants who rode a bike for three hours that same day [66]. As expected, the control group, who neither engaged in exercise nor received rhIL-6, showed elevated levels of TNF-α. Moreover, the increase of IL-6 further combats inflammation by increasing anti-inflammatory cytokines IL1ra and IL10. In turn, IL-10 down regulates pro-inflammatory cytokines TNF-a, IL-1b, IL-6, IL-1α, IL-8, and macrophage inflammatory protein-1α (MIP-1α) [63,74,76].

Further, varying exercise intensity may display different anti-inflammatory profiles in healthy individuals. For instance, Paoluccia et al. found that moderate intensity is optimal for reducing inflammation, while high-intensity training may be harmful due to perception of stress as unrecoverable [75]. In contrast, Schauer et al showed comparable anti-inflammatory effects among different intensity levels in healthy adults. However, breast cancer patients undergoing chemotherapy had decreased levels of pro-inflammatory CRP during high-intensity exercise compared to during low-to-moderate intensity exercise [79].

The few studies investigating exercise in skin diseases are limited to psoriasis and dermatomyositis (DM), where increased levels of TNF-alpha play a key role in disease progression. In psoriasis, keratinocytes proliferate in response to TNF-α, IL-17, and IFN-γ. Proliferating keratinocytes participate in a positive feedback loop, further secreting TNF-α and inducing neighboring cell proliferation [82]. Similarly, upregulation and promoter polymorphisms of TNF-alpha are associated with pathogenesis of DM [83,84]. Hence, beneficial effects of exercise seen in both psoriasis and DM may be mediated by reduction of TNF-alpha levels. Exercise is associated with reduced disease activity and improved functioning in patients with psoriasis [85]. Likewise, moderate intensity aerobic exercise is associated with improved muscle function, decreased disease activity, and higher quality of life among patients with DM [86].

CONCLUSION

This review highlights the major link between lifestyle factors and inflammatory skin disease. While there is no evidence that behavior modification should replace standard of care therapy, patients with inflammatory skin disorders may benefit from supplementing therapeutic regimens with non-pharmacological therapy in the form of altering diet, sleep, and exercise habits. Many mediators involved in pathogenesis of inflammatory disorders are those that are also shown to be downregulated during engagement in health behaviors. Of equal importance to incorporation into treatment regimens is the recognition of lifestyle behaviors as risk factors and potential screening tools for inflammatory disorders. Thus, thorough history-taking and a combination of traditional therapy with adjustment of practice in diet, sleep, and exercise will optimize holistic assessment and patient outcomes.

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